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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/881,635	06/14/2001	Peter M. Price	D6302	7258

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	7

DATE MAILED: 08/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,635	PRICE ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Claims 1-10 are pending in the application.

Election/Restrictions

1. Applicant's election without traverse of the species "drug therapy" in Paper No. 6 filed May 20, 2002 is acknowledged.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn a method for treating or preventing a pathological state of an organ in an individual by regulating the expression of the p21 gene in said organ. The pathological state can be a disorder of any organ (see claim 1) and includes any pathology, such as rejection of a transplanted organ. The claims are very broad and encompass increasing or decreasing the expression of p21. The methods of increasing or decreasing the expression of p21 are not clearly defined, and therefore encompass gene therapy (i.e. expression of exogenous p21) and antisense therapy (i.e. administration of antisense oligonucleotides to inhibit gene expression). Therefore, the nature of the invention is therapeutic gene regulation and encompasses gene therapy and antisense therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance, the broadest embodiment of the invention encompasses the treatment of any pathology of any organ in any species of animal (see claim 1).

The unpredictability of the art and the state of the prior art

Regarding gene therapy, at the time of filing the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear" (see page 409, first col.), and sites specific examples including inconsistent results, the inconsistency of results in animal models and humans, vector production problems, and vector efficiency (see page 409, columns 1-2). Specifically, regarding the ideal gene therapy vector, Crystal teaches, "The vector should be specific for its target, not recognized by the immune system, stable and easy to reproduce... Finally it would express the gene (or genes) it requires for as long as long as required in an appropriately regulated fashion." (See p. 409, second column).

Verma et al (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects).

More recently, Walther and Stein (2000) indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section). Walther and Stein also indicate, "The majority of clinical trials using viral vectors for

gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy" (See pg.267, Discussion section).

Regarding antisense therapy, Branch ("A good antisense molecule is hard to find" TIBS: February 1998, p. 45-50) teaches that there are several problems that prevent the antisense treatment of pathologies from being a predictable art. For instance, Branch teaches:

> "Antisense molecules and ribozymes capture the imagination with their rational drug design and exquisite specificity. However, they are far more difficult to produce than originally anticipated, and their ability to eliminate the function of a single gene has never been proven. Furthermore, a wide variety of non-antisense effects have come to light." (p. 45, abstract)

Branch indicates that non-antisense effects are not the only impediments to rational antisense drug design (p. 45, paragraph bridging columns 2 and 3). Specifically, Branch states, "Because biologically active compounds generally have a variety of effects, dose response curves are always needed to establish a compound's primary pharmacological identity. Antisense compounds are no exception." (see p. 46, under "All drugs are dirty: clinical benefit is the pharmaceutical gold standard"). Branch also teaches, "Because non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs. These effects must be explored on a case-by-case basis." (see p. 50, first column). Therefore, antisense therapy is unpredictable without clear evidence of a specific antisense molecule's effectiveness in vivo. Something the specification lacks.

Regarding organ transplantation, Harlan et al. (JAMA Vol. 282:1076-1082; Sept. 1999) teaches that suppression of organ transplant reject is still a challenge. For example, Harlan teaches, "Transplantation therapies have revolutionized care for patients with end stage organ (kidney, liver, heart, lung and pancreatic-beta cell) failure, yet significant problems persist with

treatments designed to prevent graft rejection. Antirejection therapies are not always effective, must be taken daily, and are both expensive and associated with well-known toxic effects." (see p. 1076, abstract). Harlan also teaches, "Indeed, the majority of kidney grafts that fail after the first year are lost to chronic graft rejection. Unfortunately, while immunologists understand the mechanisms underlying acute graft rejection in some detail, chronic rejection is less well understood and probably represents several different processes (immunological and nonimmuniological) that converge to negatively affect allograft function." (see p. 1076, paragraph bridging columns 1-2).

Additionally, the claims encompass the treatment of organ transplant rejection by eliminating the expression of the p21 gene. However, Khanna et al. (Transplantation, Vol. 67:1262-1268; 1999) teaches that cyclosporine, an immunosuppressive drug used to prevent organ transplant rejection, induces the expression of p21 (e.g., see p. 1264, Figure 2). Khanna also teaches, "Should p21 induction be a viable immunosuppressive strategy, inducing this molecule independent from the fibrogenic cytokine TGF-beta might reduce the toxicity associated with current immunosuppression." (See p. 1262, Abstract). Thus, Khanna indicates that p21 induction is associated with the immunosuppressive effects of the organ transplant rejection drug cyclosporine and induction of p21 may be a viable immunosuppressive strategy. The instant invention encompasses eliminating p21 gene expression for the therapeutic treatment of organ rejection, a notion that is contradictory to the teaching of Khanna.

To overcome the teachings in the art, the specification would need to supply direct, correlative guidance on how to administer therapeutic nucleic acids to a subject in such a way that the nucleic acid is specifically delivered to the appropriate cell (and not delivered to

undesired cells), expresses the polypeptide of interest in the cell at an appropriate level (for gene therapy), or suppresses the expression of p21 (by antisense therapy) for an appropriate duration such that administration of the nucleic acid effectively treats the organ pathology.

Working Examples and Guidance in the Specification

The specification describes mice comprising a null mutation of the p21 gene (p21(-/-)), such that the mice do not express p21. These mice are shown to be resistant to the functional and morphologic consequences of partial renal ablation, (see Examples 1-11). However, there is no indication that regulation of p21 expression would have a therapeutic effect on any/every organ pathology in any/every organ of any/every species of animal. In fact, there is no indication in the specification whatsoever indicating that regulating p21 expression in an organ has any therapeutic effect on any organ other than the kidney. Furthermore, the specification does not offer any support for regulating the expression of p21 expression for the therapeutic treatment of organ transplant rejection.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of treatment would require, initially, the identification of therapeutic molecules in animal models. Considering the breadth of the claims, gene therapy and antisense therapy molecules would have to be produced and tested in animals for efficacy. That is, for gene therapy, prior to any therapeutic intervention, it would be necessary to create a viral expression vector or plasmid which could be expressed therapeutically, show that expression of p21 occurs

in sufficient quantity and number of cells to have a therapeutic effect. For antisense therapy, a plethora of antisense molecules would have to be created and administered to test animals to determine if any of the molecules could effectively down regulate or eliminate p21 expression in the specifically desired cells and result in amelioration of the pathology; a series of showings not present in the specification. Following such experimentation, the therapy would have to be tested in human subjects to confirm the efficacy of the treatment in humans, an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy, antisense therapy, and suppression of organ transplant rejection recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
August 9, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER